CLAIMS

We claim:

1. A calcium crystal of human growth hormone or a human growth hormone derivative.

2. A monovalent cation crystal of human growth hormone or a human growth hormone derivative.

3. A protamine crystal of human growth hormone or a human growth hormone derivative.

4. A polyarginine crystal of human growth hormone or a human growth hormone derivative.

5. The monovalent cation crystal according to claim 2, wherein said monovalent cation is selected from the group consisting of: lithium, sodium, potassium and ammonium.

6. The monovalent cation crystal according to claim 5, wherein said monovalent cation is sodium.

7. The crystal according to any one of claims 1, 2, 3 or 4, wherein a single administration of said crystal to a mammal provides an *in vivo* hGH serum concentration in said mammal selected from the group consisting of:

(a) between about 0.3 ng/ml to about 2,500 ng/ml hGH;

(b) between about 0.5 ng/ml to about 1,000 ng/ml hGH; and

(c) between about 1 ng/ml to about 100 ng/ml hGH, for a time period selected from the group consisting of:

(i) between about 0.5 hours and about 40 days post-administration;

(ii) between about 0.5 hours and about 10 days post-administration;

(iii) between about 0.5 hours and about 7 days post-administration; and

(iv) between about 0.5 hours and about 1 day post-administration.

8. The crystal according to any one of claims 1, 2, 3 or 4, wherein a single administration of said crystal to a mammal provides an *in vivo* IGF-1 serum elevation over baseline IGF-1 level in said mammal prior to said administration selected from the group consisting of:

(a) between about 5 ng/ml to about 2,500 ng/ml; and

(b) between about 100 ng/ml to about 1,000 ng/ml,

for a time period selected from the group consisting of:

(i) between about 0.5 hours and about 40 days post-administration; and

(ii) between about 0.5 hours and about 7 days post-administration.

9. The crystal according to any one of claims 1, 2, 3 or 4, wherein said crystal has a relative bioavailability of at least 50% or more, as compared to that of an identical dose of soluble hGH delivered via the same administrative route, wherein said bioavailability is measured by AUC of total *in vivo* hGH serum concentration for said soluble hGH and said crystal.

10. The crystal according to claim 7 or 8, wherein said mammal is a human.

11. The crystal according to claim 1, wherein said crystal comprises from about 1 to about 500 calcium molecules per monomer of human growth hormone or human growth hormone derivative.

12. The crystal according to claim 2, wherein said crystal comprises from about 1 to about 500 monovalent cations per monomer of human growth hormone or human growth hormone derivative.

13. The crystal according to claim 1, wherein said crystal comprises a calcium salt selected from the group consisting of: calcium acetate, calcium chloride, calcium sulfate and calcium gluconate.

14. The crystal according to claim 13, wherein said calcium salt is calcium acetate.

15. The crystal according to claim 6, wherein said crystal comprises a sodium salt selected from the group consisting of: sodium citrate, sodium phosphate and sodium acetate.

16. The crystal according to claim 15, wherein said sodium salt is sodium acetate.

17. A composition comprising crystals of human growth hormone or a human growth hormone derivative and an excipient, wherein said crystals are selected from the group consisting of:

(a) calcium crystals of human growth hormone or a human growth hormone derivative;

(b) monovalent cation crystals of human growth hormone or a human growth hormone derivative;

(c) protamine crystals or human growth hormone or a human hormone derivative; and

(d) polyarginine crystals of human growth hormone or a human growth hormone derivative.

18. The composition according to claim 17, wherein said crystals and said excipient are present in said composition

at a molar ratio of hGH:excipient of about 1:10 to about 1:0.125.

19. The composition according to claim 17, wherein said excipient is selected from the group consisting of: amino acids, salts, alcohols, carbohydrates, proteins, lipids, surfactants, polymers, polyamino acids and mixtures thereof.

20. The composition according to claim 19, wherein said excipient is selected from the group consisting of: protamine, polyvinylalcohol, cyclodextrins, dextrans, calcium gluconate, polyamino acids, polyethylene glycol, dendrimers, polyorthinine, polyethyleneimine, chitosan and mixtures thereof.

21. The composition according to claim 20, wherein said excipient is selected from the group consisting of: protamine, polyarginine, polyethylene glycol and mixtures thereof.

22. The composition according to claim 17, wherein the concentration of human growth hormone or human growth hormone derivative in said composition is selected from the group consisting of:

(a) between about 0.1 and about 100 mg/ml;

(b) between about 1 and about 100 mg/ml; and

(c) between about 10 and about 100 mg/ml.

23. A method for treating a mammal having a disorder associated with human growth hormone deficiency or which is ameliorated by treatment with human growth hormone, comprising the step of administering to said mammal a therapeutically effective amount of a crystal according to any one of claims 1, 2, 3 or 4, or composition according to claim 17.

24. A method for inducing weight gain in a mammal, comprising the step of administering to said mammal a therapeutically effective amount of a crystal according to any one of claims 1, 2, 3 or 4, or a composition according to claim 17.

25. The method according to claim 24, wherein said mammal is a hypophysectomized rat and the weight gain induced in said rat is between 5% and about 40% following administration of said crystals by injection once a week.

26. The method according to claim 23, wherein said disorder is selected from the group consisting of: adult growth hormone deficiency, pediatric growth hormone deficiency, Prader-Willi syndrome, Turner syndrome, short bowel syndrome, chronic renal insufficiency, idiopathic short stature, dwarfism, hypopituitary dwarfism, bone regeneration, female infertility, intrauterine growth retardation, AIDS-related cachexia, Crohn's disease and burns.

27. The method according to claim 26, wherein said disorder is pediatric growth hormone deficiency and said method results in annualized growth velocity in said mammal of between about 7 and about 11 cm.

28. The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by oral route, parenteral route, subcutaneous route or intramuscular route.

29. The method according to claim 28, wherein said crystal or composition is administered to said mammal by subcutaneous route using a needle having a gauge greater than or equal to 27.

30. The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by needle-free injection or meta dose infusion pump.

31. The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by a time regimen selected from the group consisting of:

(a) about once every three days;

(b) about once a week;

(c) about once every two weeks; and

(d) about once every month.

32. The method according to claim 23 or 24, wherein said mammal is a human.

33. A method for producing calcium crystals, monovalent cation crystals, protamine crystals or polyarginine crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization solution, said crystallization solution comprising a calcium salt or a monovalent cation salt and an ionic polymer, wherein said ionic polymer is protamine or polyarginine; and

(b) incubating said crystallization solution for greater than about 12 hours at a temperature between about 4°C and about 37°C, until calcium crystals, monovalent cation crystals, protamine crystals or polyarginine crystals of human growth hormone or a human growth hormone derivative are produced.

34. The method according to claim 33, wherein said ionic polymer is polylysine.

35. The method according to claim 33, wherein said ionic polymer is a mixture of any two or more of protamine, polyarginine and polylysine.

36. A method for producing calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization buffer to produce a crystallization solution;

(b) adding deionized water to said crystallization solution;

(c) adding a precipitant to said crystallization solution;

(d) adding a calcium salt or a monovalent cation salt to said crystallization solution;

(e) incubating said crystallization solution for between about 2 and about 168 hours at a temperature between about 10°C and about 40°C, until calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative are formed; and

(f) adding an ionic polymer or an ionic small molecule to said calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative.

37. A method for producing calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization buffer to produce a crystallization solution;

(b) adding deionized water to said crystallization solution;

(c) adding an ionic small molecule or an ionic polymer to said crystallization solution;

(d) adding a calcium salt or monovalent cation salt to said crystallization solution; and

(e) incubating said crystallization solution for between about 2 and about 168 hours at a temperature between about 10°C and about 40°C, until calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative are formed.

38. The method according to claim 37, wherein, following step (b) and prior to step (c), said method comprises the step of: adding a precipitant to said crystallization solution.

39. The method according to any one of claims 33, 36 or 37, wherein said calcium salt is selected from the group consisting of: calcium acetate, calcium chloride, calcium gluconate and calcium sulfate.

40. The method according to claim 39, wherein said calcium salt is calcium acetate.

41. The method according to any one of claims 33, 36 or 37, wherein said monovalent cation is selected from the group consisting of: lithium, sodium, potassium and ammonium.

42. The method according to claim 41, wherein said monovalent cation is sodium.

43. The method according to any one of claims 33, 36 or 37, wherein said monovalent cation salt is selected from the group consisting of: sodium citrate, sodium phosphate and sodium acetate.

44. The method according to claim 43, wherein said monovalent cation salt is sodium acetate.

45. The method according to claim 33, wherein said crystallization solution further comprises a pH buffer.

46. The method according to claim 45, wherein said pH buffer is a buffer selected from the group consisting of: Tris, HEPES, acetate, phosphate, citrate, borate, imidazole and glycine.

47. The method according to claim 36 or 38, wherein said precipitant is a non-ionic small molecule or a non-ionic polymer.

48. The method according to claim 47, wherein said non-ionic polymer is selected from the group consisting of: polyethylene glycol, polyvinyl alcohol and mixtures thereof.

49. The method according to claim 48, wherein said polyethylene glycol is present in said crystallization solution at a concentration between about 0.5% and about 20% (w/v).

50. The method according to claim 36 or 38, wherein said precipitant is selected from the group consisting of: amino acids, peptides, polyamino acids and mixtures thereof.

51. The method according to any one of claims 33, 36 or 37, wherein said human growth hormone or human growth hormone derivative is present in said crystallization solution at a concentration selected from the group consisting of:

(a) a concentration between about 1 mg/ml and about 1,000 mg/ml;

(b) a concentration between about 2 mg/ml and about 50 mg/ml; and

(c) a concentration between about 10 mg/ml and about 25 mg/ml.

52. The method according to any one of claims 33, 36 or 37, wherein said calcium salt or said monovalent cation salt is present in said crystallization solution at a concentration selected from the group consisting of:

(a) a concentration between about 0.01 and about 1 M; and

(b) a concentration between about 25 and about 205 mM.

53. The method according to any one of claims 33, 36 or 37, wherein said crystallization solution is incubated for a time and a temperature selected for the group consisting of:

(a) between about 0.25 day and about two days at a temperature of about 33°C;

(b) between about 0.25 day and about two days at a temperature of about 25°C; and

(c) between about 0.25 day and about two days at a temperature of about 15°C.

54. The method according to claim 36 or 37, wherein said ionic small molecule is selected from the group consisting of: amino acids, peptides and mixtures thereof.

55. The method according to claim 36 or 37, wherein said ionic polymer is selected from the group consisting of: protamine, polysaccharides, polyamino acids, polyarginine, polylysine, polyglutamate, dendrimers, polyorthinine, polyethyleneimine, chitosan and mixtures thereof.

56. The method according to claim 55, wherein said ionic polymer is protamine or polyarginine.

57. The method according to claim 36 or 37, wherein said crystallization buffer is selected from the group consisting of: Tris-HCl buffer, glycine buffer, HEPES buffer, imidazole buffer, Bis-Tris buffer, AMP, AMPD, AMPSO, bicine, Ethanolamine, glyclglycine, TAPS, Taurin, Triane and mixtures thereof.

58. The method according to claim 36 or 37, wherein, in step (a) of claim 36 or step (a) of claim 37, said crystallization buffer is present in said crystallization solution at a concentration between about 10 mM and about 800 mM.

59. The method according to claim 44, wherein, in step (e) of claim 36 or step (e) of claim 37, said sodium acetate is present in said solution at a concentration selected from the group consisting of:

(a) a concentration between about 0.5 mM and about 800 mM; and

(b) a concentration between about 100 mM and about 500 mM.